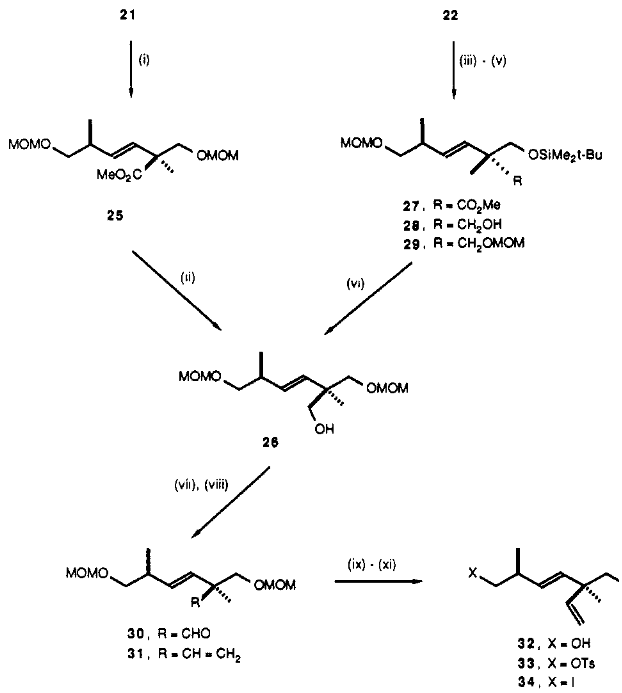
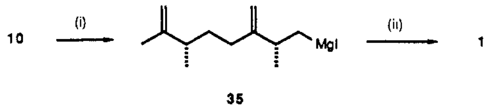
Scheme IV[a]



[a](i) $ClCH_2OCH_3$, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, room temeprature, 4 h, 98%; (ii) $LiAlH_4$, Et_2O, room temperature, 4 h, 98%; (iii) t-$BuMe_2SiCl$, imidazole, DMF, room temperature, 18 h, 93%; (iv) $(i\text{-}Bu)_2AlH$, Et_2O, room temperature, 4 h, 70%; (v) $ClCH_2OCH_3$, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, room temperature, 4 h, 79%; (vi) Bu_4NF, THF, room temperature, 2 h, 73%; (vii) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, then Et_3N, 1 h, 60%; (viii) Ph_3PCH_2, THF, 0 °C, 1 h, then room temperature, 1 h, 70%; (ix) concentrated HCl catalyst, MeOH, Δ, 1 h, 99%; (x) p-TsCl, py, 0 °C, 24 h, then room temperature, 24 h, 74%; (xi) NaI, CH_3COCH_3, Δ, 18 h, then in 2-butanone, Δ, 48 h, 63%.

Scheme V[a]



[a](i) Mg, THF, Δ, 6 h; (ii) CuI, THF, then **34**, room temperautre, 5 days, 33–42%.

26 under Swern conditions afforded aldehyde **30** which was transformed to **31** in a Wittig reaction. This diene was unmasked to yield **32**, and the latter was converted to diiodide **34** via its bis tosylate **33**.

The union of 2 equiv of **10** with **34** was investigated under a variety of conditions, and, although coupling could be effected rapidly at the sterically less encumbered terminus of **34**, the neopentyl iodide proved to be extremely sluggish in its reactivity. Eventually, it was found that preparation of Grignard reagent **35**, followed by treatment with anhydrous cuprous iodide, afforded an alkylcopper species[13] that underwent slow reaction with **34** to give botryococcene (**1**) (see Scheme V). The synthetic material was identical with the natural hydrocarbon in all respects, including optical rotation. This first synthesis of a member of the botryococcene family, together with the stereochemical investigation completed earlier,[5] sets the stage for biogenetic and other studies of this intriguing class of terpenoids.

Acknowledgment. We are indebted to Professor Arthur G. Schultz for providing unpublished information and to Professor Douglas A. Keszler for assistance with the X-ray crystal structure determination. Finanical support for this research was provided by the National Science Foundation (CHE-8619029) and by the Petroleum Research Fund, administered by the American Chemical Society, through a Summer Research Fellowship to G.O.S. Funds for the purchase of a Bruker AM 400 NMR spectrometer and a Rigaku X-ray diffractometer were provided by the National Science Foundation.

Supplementary Material Available: Spectral data are available for compounds **1, 3–7, 9, 10, 12–15, 18, 19, 21, 22, 24–31**, and **33** (8 pages). Ordering information is given on any current masthead page.

(13) Tamura, M.; Kochi, J. *J. Am. Chem. Soc.* **1971**, *93*, 1485.

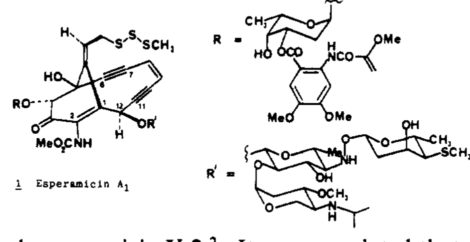
A Model for the Proposed Mechanism of Action of the Potent Antitumor Antibiotic Esperamicin A_1

Philip Magnus* and Paul A. Carter

Department of Chemistry, Indiana University
Bloomington, Indiana 47405

Received November 19, 1987

Very recently two groups reported the extraordinary structures of a new class of extremely potent antitumor antibiotics, of which esperamicin A_1 **1** has the common aglycone bicyclo[7.3.1]diynene system.[1] Co-occurring with these metabolites is an inactive



compound, esperamicin X **2**.[2] It was speculated that the mode of biological action of **1** involves nucleophilic attack on the central sulfur atom and thiol addition to the α,β-unsaturated carbonyl group to give the putative intermediate **3** (see Scheme I). It was suggested that the change of hybridization at C-1 from sp^2 to sp^3, in effect, pulls together the ends of the diynene C-6 and C-11 to allow cyclization of the diynene **3** into the 1,4-diyl(p-benzyne) **4**. This diradical can abstract a hydrogen atom from the sugar phosphate backbone of DNA and result in strand scission. While **3** can cyclize to the [3.3.1]system **4**, esperamicin **1** cannot, since the transition state would be prohibitively high due to the bridgehead double bond at C-1. Consequently, the triggering thiol addition at C-1 does more than reduce the distance between C-6 and C-11, it allows access to a reasonable kinetic pathway to **4**. The 1,4-diyl process has a parallel in the earlier work of Bergman,[3] who showed that the prototype diynene **5** could be converted into benzene and 1,4-dichlorobenzene when exposed to 1,4-cyclohexadiene and CCl_4, respectively. The conditions (195 °C) hardly parallel the mild conditions (room temperature to 37 °C) speculated for the conversion of **3** into **4**. The $\Delta G^{\ddagger}$ for the conversion of **5** into benzene via the 1,4-diyl is approximately 32 kcal mol^{-1}.

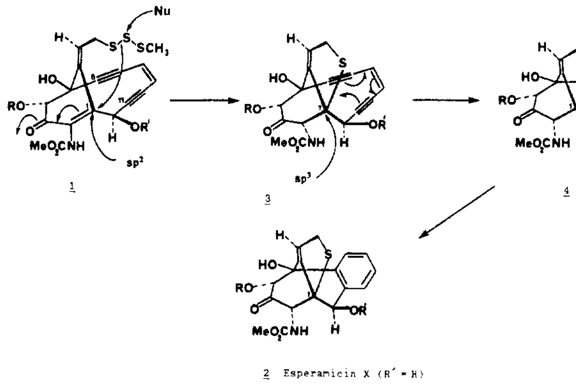
(1) Golik, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K-i.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462. Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. This latter reference describes the calichemicins: Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466.

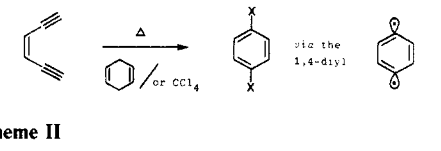
(2) Golik, J.; Clardy, J.; Dubay, G.; Groenewold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkuma, H.; Saitoh, K.-i; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461.

(3) Bergman, R. G. *Acc. Chem. Res.* **1973**, *6*, 25. Lockhart, T. P.; Comita, P. B.; Gergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4082. Lockhart, T. P.; Bergman, R. G. *J. Am. Chem. Soc.* **1981**, *103*, 4091. Jones, R. R.; Bergman, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 660. The conversion of diynenes into antisymmetric benzene-1,4-diyl is a symmetry-allowed process: Hoffman, R.; Imamura, A.; Hehre, W. J. *J. Am. Chem. Soc.* **1968**, *90*, 1499. Dewar, M. J. D.; Li, W-K. *J. Am. Chem. Soc.* **1974**, *96*, 5569. For biradical reactivity, see: Chapman, O. L.; Chang, C. C.; Kole, J. *J. Am. Chem. Soc.* **1976**, *98*, 5703. Darby, N.; Kim, C. U.; Salaun, J. A.; Shelton, K. W.; Takeda, S.; Masamune, S. *J. Chem. Soc. D.* **1971**, 1516. Wong, H. N. C.; Sondheimer, F. *Tetrahedron Lett.* **1980**, *21*, 217.

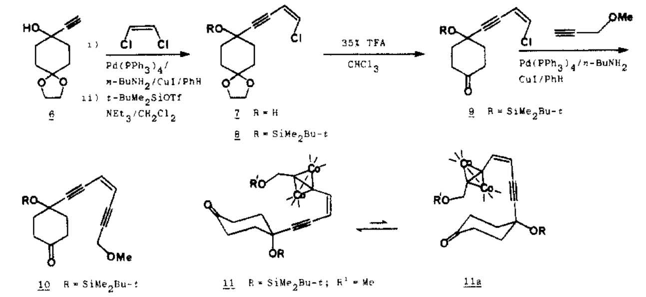
0002-7863/88/1510-1626$01.50/0

Scheme I





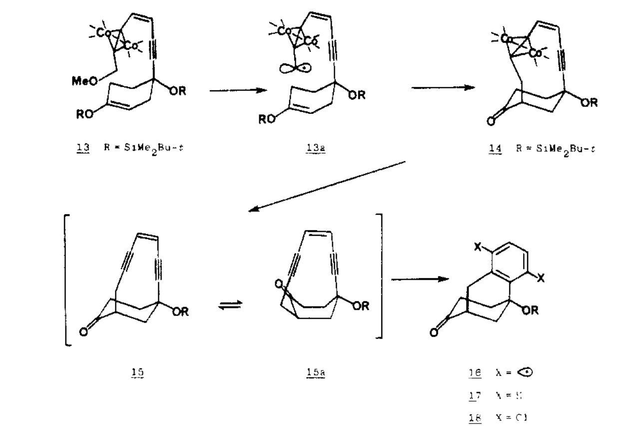
Scheme II



Benzene-1,4-diyl is only 14 kcal mol^{-1} in energy above the diynene **5**. Consequently, the strain energy in **3** must be sufficient to overcome the potential activation energy of 32 kcal mol^{-1} at ambient temperatures. This requires that the release of strain energy going from **3** to **2** should be at least 10–12 kcal mol^{-1} in order to proceed at a reasonable rate at room temperature. With this in mind, we have constructed a model system that maintains C-1 as sp^3 hybridized yet prevents cyclization into the diyl, because one of the triple bonds is complexed as its derived dicobalt hexacarbonyl metallocycle.[4] This device allows us to examine the release of the diynene by oxidation and the cyclization to a 1,4-diyl in the absence of the initiating thiol chemistry. In the course of their studies on calichemicins,[1] the Lederle group has converted the analogue of **1** into the calichemicin analogue of **2** and observed deuterium incorporation into the para positions of the aromatic ring when this transformation was carried out in the presence of CD_2Cl_2.

Treatment of cyclohexane-1,4-dione monoketal with lithium acetylide gave **6** (66%), which was coupled with (*Z*)-dichloroethylene with use of $Pd(PPh_3)_4/CuI/n\text{-}BuNH_2/PhH$ to give **7** (65%) (see Scheme II). Protection ($t\text{-}BuMe_2SiOTf/NEt_3/CH_2Cl_2$) of **7** as its *tert*-butyldimethylsilyl ether **8** (82%) and mild acid hydrolysis of **8** gave **9** (88%). Coupling ($Pd(PPh_3)_4/CuI/n\text{-}BuNH_2/PhH$) with propargyl methyl ether gave **10** (74%).[5] As expected, when **10** was treated with $Co_2(CO)_8$ (1.0 equiv) in heptane the least hindered acetylene was converted into the dicobalt hexacarbonyl cluster **11** (82%). The structure of **11** was unambiguously confirmed by a single-crystal X-ray structure of the alcohol **12**.[6] This shows that in the solid state the linear acetylene portion occupies an equatorial conformation. The compound **11** can only cyclize via the propargyl cation in the axial conformation **11a**. Treatment of **11** with $t\text{-}BuMe_2SiOTf/NEt_3/CH_2Cl_2$ gave **13** (89%). When **13** was exposed to $TiCl_4$ (6 equiv)/DABCO (1 equiv) at −78 °C, followed by warming to −50 °C, the cyclized product **14** (45%) was obtained as a stable compound[7] (see Scheme III). The ^{1}H NMR showed that the methyl groups attached to Si are no longer equivalent due to hindered rotation. Oxidative decomplexation of **14** in 1,4-cyclohexadiene using *N*-methylmorpholine *N*-oxide[8] at 20 °C rapidly gave **17** (50%). Similarly, conducting the same decomplexation in $CCl_4/t\text{-}BuOH$ gave **18** (29%).[9] We could not detect the intermediate diynene **15**. It is important to note that the acyclic enediyne dicobalt hexacarbonyl adduct **11** can be oxidatively decomplexed to give the enediyne **10** *without* aromatization. Therefore, we believe that the conversion of **14** via **15** into **16** is *not* complicated by a cobalt-catalyzed process and proceeds via the decomplexed enediyne **15**. Molecular models of **14** show that the $Co_2(CO)_6$ cluster locks **14** in the conformation shown, which also corresponds to the one needed (**13a**) to arrive at **14**. This is because the usual linear acetylene is bent in the $Co_2(CO)_6$ cluster from 180° to approximately 145°.[8] When the $Co_2(CO)_6$ residue to oxidatively removed it should directly generate **15**, which is the higher energy conformer needed to produce the diyl **16**. The linear ynes in **15** are more strained than in **15a** where the cyclohexyl ring is in a boat conformation. MMX calculations, which are parameterized to allow for the weak sp bending modes, suggest that **15** is approximately 3 kcal mol^{-1} more strained than **15a**. Comparing the differences in potential energies between **15a** and **17** (the *t*-OR substituent is removed) and between **5** and benzene or the 1,6-dimethyl analogue of **5**, into *o*-xylene, it was found that overall there is an 8.8 kcal mol^{-1} lowering of $\Delta H^{\ddagger}$ for the conversion of **15a** into **17** relative to the references.[10] This means

Scheme III



(4) Sly, W. G. *J. Am Chem. Soc.* **1959**, *81*, 18. Gregson, D.; Howard, J. A. K. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1983**, *C39*, 1024.

(5) Coupling procedures follow literature methods, see: Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1984**, *25*, 6001. Guillerm, D.; Linstrumelle, G. *Tetrahedron Lett.* **1986**, *27*, 5857. These authors report the synthesis of the diynene i, which is a stable lactone: Guillerm, D.; Linstrumelle, G. *Tetrahedron Lett.* **1985**, *26*, 3811. Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1981**, *22*, 207. Stephans, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313.

(6) The complete details of the single-crystal X-ray structural determination of **12** may be obtained from Dr. John Huffman, Molecular Structure Center, Indiana University, IN 47405. Please ask for structure report no. 87190.

(7) The propargyl cation chemistry has recently been reviewed: Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207. Nicholas, K. M.; Mulraney, M.; Bayer, M. *J. Am. Chem. Soc.* **1980**, *102*, 2508. Schreiber, S. L.; Sammakia, T.; Crowe, W. E. *J. Am. Chem. Soc.* **1986**, *108*, 3128. Schreiber, S. L.; Klimas, M. Y.; Sammakia, T. *J. Am. Chem. Soc.* **1987**, *109*, 5749.

(8) Magnus, P.; Becker, D. P. *J. Chem. Soc., Chem. Commun.* **1985**, 640.

(9) Compound **17** (X = H; R = H) is known: Hook, J. M.; Mander, L. N. *J. Org. Chem.* **1980**, *45*, 1722.)

(10) Here the aromatic material is used as a model for the transition state leading to the diyl. The MMX calculations used the VESCF π routines from MM1 (QCPE no. 318) to adjust unsaturated carbon distances. The rest of the force field in MMX is similar to that in MM2, except for sp carbon bending force constants being one third the MM2 values. The stiffer sp bending constants in MM2 give a 3.5 kcal/mol higher strain energy in **15a**. The potential energy of (*Z*)-bis(1^1-propynyl)ethene is −3.47 kcal/mol and *o*-xylene is 9.77 kcal/mol; the value for **15a** is 16.27 kcal/mol and that for **17** is 20.7 kcal/mol. MMX is available from Serena Software.

that E_{act} for the conversion of **15a** into **17** is approximately 18.6 kcal mol^{-1} ($t_{1/2}$ 334 s at 300 K). Thus we have demonstrated that the diynene **15** is sufficiently strained that even at room temperature it undergoes rapid cyclization into the 1,4-diyl **16**. The products **17** and **18** are clear indications of a radical abstraction process and provide substantial vindication of the proposed mechanism. We are currently pursuing more elaborate models that contain the C-12 oxygen substituent and the C-13,14-double bond.[11]

Acknowledgment. The National Institutes of Health are gratefully thanked for their support. Dr. Terry Doyle (Bristol-Myers) is thanked for helpful discussions. Dr. John Huffman, Molecular Structure Center, Indiana University, Bloomington, IN 47405, is thanked for the X-ray structural determinations. Dr. J. Gajewski is thanked for carrying out the MMX calculations and discussions on the above problems.

(11) NMR data for **10**, **11**, **14**, and **17** are as follows. **10**: ^{1}NMR (300 MHz, $CDCl_3$) δ 5.86 (2 H, m), 4.21 (2 H, d, J = 1.8 Hz), 3.36 (3 H, s), 2.50 (4 H, m), 2.14 (4 H, t, J = 6.9 Hz), 0.87 (9 H, s), 0.21 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.68 (s), 119.57 (d), 118.81 (d), 98.75 (s), 92.90 (s), 83.40 (s), 83.01 (s), 67.75 (s), 60.21 (t), 57.61 (q), 40.14 (t), 37.40 (t), 25.80 (q), 18.13 (s), −3.00 (q). **11**: ^{1}H NMR (300 MHz, C_6D_6) δ 6.32 (1 H, d, J = 11.0 Hz), 5.50 (1 H, d, J = 11.0 Hz), 4.59 (2 H, s), 3.19 (3 H, s), 2.55 (2 H, m), 2.23 (2 H, m), 1.8–2.1 (2 H, m), 0.95 (9 H, s), 0.22 (6 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.77 (s), 198 (m), 136.82 (d), 109.84 (d), 102.22 (s), 94.18 (s), 83.39 (s), 81.76 (s), 73.38 (t), 67.44 (s), 58.99 (q), 39.74 (t), 37.18 (t), 25.85 (q), 18.40 (s), −2.84 (q). **14**: ^{1}H NMR (300 MHz, C_6D_6) δ 6.88 (1 H, d, J = 9.4 Hz), 5.64 (1 H, d, J = 9.4 Hz), 3.20 (3 H, m), 2.7 (2 H, m), 2.3 (4 H, m), 0.92 (9 H, s), 0.26 (3 H, s); 0.18 (3 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.52 (s), 198.74–199.13 (m), 142.69 (d), 109.50 (d), 102.70 (s), 99.28 (s), 88.63 (s), 83.11 (s), 69.78 (s), 56.64 (d), 45.42 (t), 41.09 (t), 36.81 (t), 35.36 (t), 25.84 (q), 18.28 (s), −3.10 (q). **17**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.19 (4 H, m), 3.37 (1 H, dd, J's = 9.0 and 17.4 Hz), 2.82 (1 H, m), 2.67 (1 H, dd, J's = 6.2 and 15.7 Hz), 2.59 (1 H, m), 2.52 (1 H, dd, J's = 5.2 and 17.4 Hz), 2.31 (2 H, m), 2.16 (2 H, m), 0.87 (9 H, s), −0.06 (3 H, s), −0.19 (3 H, s).

Does Dehydroquinate Synthase Synthesize Dehydroquinate?

Paul A. Bartlett* and Kunio Satake

Department of Chemistry, University of California
Berkeley, California 94720

Received November 2, 1987

The biosynthetic conversion of 3-deoxy-D-*arabino*-heptulosonic acid 7-phosphate (DAHP) to 3-dehydroquinic acid (DHQ), attributed to 3-dehydroquinate synthase (EC 4.6.1.3), occurs at an early stage of the shikimate pathway.[1] The mechanistic details of the transformation (Scheme I)[2] reflect both clever functional group manipulation and stereochemical dexterity on the part of the enzyme. Temporary introduction of a ketone at C-5 of DAHP facilitates elimination of phosphate and generation of an enolpyranose **3**. From this intermediate, ring opening and rotation of the ensuing acyclic enol or enolate (→ **4**) set the stage for ring closure via an aldol condensation to provide the observed product, DHQ. We report here the nonenzymatic generation of enolpyranose **3** and observations of its chemical behavior which suggest that its biosynthetic conversion to DHQ may not be an enzyme-catalyzed process.

The enolpyranose **3** was expected to be unstable both toward isolation as well as under acidic or basic conditions typically

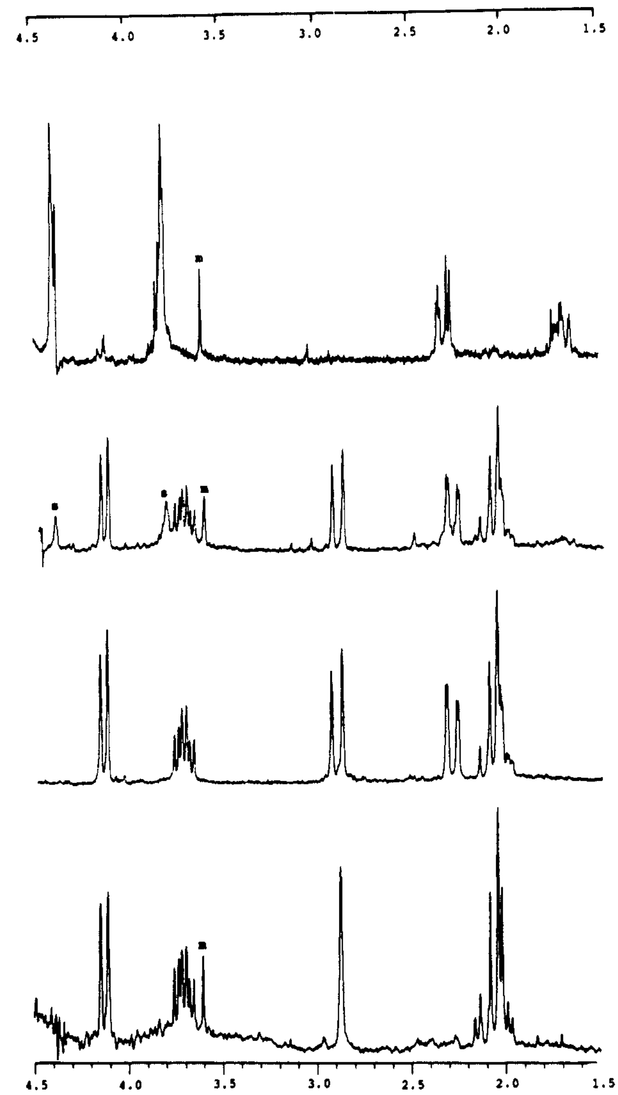
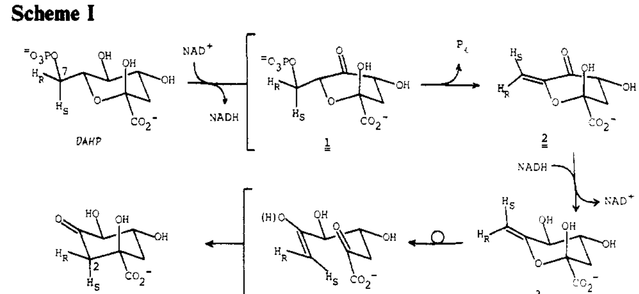


Figure 1. (a) There is 5.6 mg of **15** in 0.65 mL of 0.1 M phosphate buffer (0.39 mmol of NaH_2PO_4 and 0.61 mmol of Na_2HPO_4 in 10.0 mL of D_2O): m = methanol. (b) Solution from (a) after irradiation for 15 min at 0 °C: m = methanol, s = residual **15**. (c) Authentic DHQ in phosphate buffer. (d) Solution from irradiation of (7Z)-(7-^{2}H)-**15** (94% stereoisomeric purity) under the same conditions as (a): m = methanol.

Scheme I



utilized for removal of hydroxyl- or ketal-protecting groups. *o*-Nitrobenzyl ketal **15** was therefore chosen as the immediate precursor to **3**, since deprotection could be accomplished photochemically under neutral conditions.[3] This intermediate was synthesized from methyl 3-deoxy-D-*arabino*-heptulosonate, **5**,[4] as shown in Scheme II.[5]

(1) Weiss, U.; Edwards, J. M. *The Biosynthesis of Aromatic Compounds*; Wiley: New York, 1980. Ganem, B. *Tetrahedron* **1978**, *34*, 3353. Haslam, E. *The Shikimate Pathway*; Wiley: New York, 1974.

(2) (a) Rotenberg, S. L.; Sprinson, D. B. *J. Biol. Chem.* **1978**, *253*, 2210–15. Maitra, U. S.; Sprinson, D. B. *J. Biol. Chem.* **1978**, *253*, 5426–30. (b) Turner, M. J.; Smith, B. W.; Haslam, E. *J. Chem. Soc., Perkin Trans. 1* **1975**, 52–55. (c) Le Maréchal, P.; Azerad, R. *Biochimie* **1976**, *58*, 1123–28. (d) Lambert, J. M.; Boocock, M. R.; Coggins, J. R. *Biochem. J.* **1985**, *226*, 817. (e) Widlanski, T. S.; Bender, S. L.; Knowles, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 1873–1875.

(3) Zehavi, E.; Amit, B.; Patchornik, A. *J. Org. Chem.* **1972**, *37*, 2281. Zehavi, E.; Patchornik, A. *J. Org. Chem.* **1972**, *37*, 2285.

(4) Compound **5** was prepared by Dowex 50W X8-catalyzed hydrolysis of the corresponding diacetonide as described in the following: Frost, J. W.; Knowles, J. R. *Biochemistry* **1984**, *23*, 4465–4469.

0002-7863/88/1510-1628$01.50/0